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MEDICAL DEVICES ADVISORY COMMITTEE

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GENERAL AND PLASTIC SURGERY

DEVICES PANEL

* * *

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been edited and FDA
makes no representation
regarding its accuracy

Wednesday, January 12, 2000

* * *

The meeting took place at 10:00 a.m., in
Conference Room 020B, Center for Devices and
Radiologic Health, 9200 Corporate Boulevard,
Rockville, Maryland, Dr. Thomas V. Whalen, Panel
Chair, presiding.

PRESENT:

THOMAS V. WHALEN, M.D., Panel Chair
DAVID L. DeMETS, Ph.D., Voting Member
ROBERT L. McCAULEY, M.D., Voting Member
MARY E. DAVIS, Ph.D., Temporary Voting Member
CHARLES E. EDMISTON, JR., Ph.D., Temporary
Voting Member
BARBARA LEVY, M.D., Temporary Voting Member
SUBIR ROY, M.D., Temporary Voting Member
MARK A. TALAMINI, M.D., Temporary Voting Member

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PRESENT (Continue):

MAXINE F. BRINKMAN, R.N., Consumer

Representative

MARCIA YAROSS, Ph.D., Industry Representative

APPLICANT PRESENTERS:

GEORGIANN KEYPORT, M.S. RAC

DOUGLAS B. JOHNS, Ph.D.

GERE diZEREKA, M.D.

FDA PRESENTERS:

STEPHEN P. RHODES

DAVID KRAUSE, Ph.D.

ROXOLANA HORBOWYJ, M.D.

RICHARD KOTZ, Ph.D.

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C O N T E N T SPAGE

Conflict of Interest Statement	14
Temporary Voting Status Statement	16
Introductions	17
Lifecore Biomedical, INTERGEL Adhesion Prevention Solution:	
Introduction	24
Results of Randomized Clinical Study	27
Safety Profile	50
FDA Presentation:	
Preclinical and Technical Aspects	96
Clinical Aspects	103
Statistical Aspects	121
FDA Questions to the Panel	132
Panel Discussion	135
Panel Responses to FDA Questions	162
Final Comments by Lifecore	197
Public Comment	187
Vote of Panel	208

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P R O C E E D I N G S

(10:34 a.m.)

DR. KRAUSE: Okay. I'd like to start the open session of today's panel meeting.

Good morning, everyone. We're ready to begin the 55th meeting of the General and Plastic Surgery Devices Panel.

My name is David Krause, and I'm the Executive Secretary of this panel and a reviewer in the Plastic and Reconstructive Surgery Devices Branch in the Division of General and Restorative Devices.

I'd like to remind everyone that you are requested to please sign in on the attendance sheets which are available at the tables just outside the doors. You may also pick up an agenda, a panel meeting roster, and information about today's meeting at the same place, just outside the doors.

The information includes how to find out about future meetings and future meeting dates through the Advisory Panel phone line and how to obtain meeting minutes or transcripts.

Before turning the meeting over to Dr.

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1 Whalen, I'm required to read two statements into the
2 record. One is the deputization of temporary voting
3 members, and the other is the conflict of interest
4 statement. So I'm going to start with the temporary
5 -- actually with the conflict of interest statement.

6 The following announcement addresses
7 conflict of interest issues associated with this
8 meeting and is made a part of the record to preclude
9 even the appearance of an impropriety.

10 To determine if any conflict existed, the
11 agency reviewed the submitted agenda and all financial
12 interests reported by the committee participants. The
13 conflict of interest statutes prohibit special
14 government employees from participating in matters
15 that could affect their or their employer's financial
16 interests.

17 However, the agency has determined that
18 participation of certain members and consultants, the
19 need for whose services outweighs the potential
20 conflict of interest involved in the best interest of
21 the government.

22 Waivers have been granted for Drs. David

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1 DeMets and Mark Talamini for their interest in firms
2 at issue that could potentially be affected by the
3 committee's deliberations. The waiver allows these
4 individuals to participate fully in today's
5 deliberations.

6 A copy of these waivers may be obtained
7 from the agency's Freedom of Information Office, Room
8 12A-15 of the Parklawn Building.

9 We would like to note for the record that
10 the agency took into consideration certain matters
11 regarding Drs. Barbara Levy, Robert McCauley, David
12 DeMets, Subir Roy, and Mark Talamini. Each of these
13 panelists reported past and/or current interest in
14 firms at issue, but not in matters related to what is
15 being discussed today.

16 Since these interests are not related to
17 the specific issue before the panel, the agency has
18 determined that they may participate fully in today's
19 deliberations.

20 In the event that the discussions involve
21 any other products or firms not already on the agenda
22 for which an FDA participant has a financial interest,

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1 the participant should excuse him or herself from such
2 involvement, and the exclusion will be noted for the
3 record.

4 With respect to all other participants, we
5 ask in the interest of fairness that all persons
6 making statements or presentations disclose any
7 current or previous financial involvement with any
8 firm whose products they may wish to comment upon.

9 The second statement is the appointment to
10 temporary voting status. The statement is signed by
11 Dr. Feigal. I will be reading it in the first person.
12 So it's not me saying this. It's Dr. Feigal.

13 "Pursuant to the authority granted under
14 the Medical Devices Advisory Committee charters, dated
15 October 27th, 1990, and as amended August 18th, 1999,
16 I appoint the following individuals as voting members
17 of the General and Plastic Surgery Devices Panel for
18 this meeting on January 12th, 2000: Mary E. Davis,
19 Charles E. Edmiston, Barbara Levy, Subir Roy, Mark A.
20 Talamini.

21 "For the record, these individuals are
22 special government employees and consultants to this

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1 panel or other panels under the Medical Devices
2 Advisory Committee. They have undergone the customary
3 conflict of interest review and have reviewed the
4 material to be considered at this meeting."

5 Thank you.

6 Okay. At this point I'd like to turn the
7 meeting over to Dr. Whalen.

8 CHAIRMAN WHALEN: Thank you, Dr. Krause.

9 Good morning. I'm Dr. Thomas Whalen. I'm
10 Associate Professor of Surgery and Pediatrics at
11 Robert Wood Johnson Medical School and a pediatric
12 surgeon in Camden, New Jersey. I am the chairperson
13 for this panel.

14 Today we will be making recommendations to
15 the Food and Drug Administration on a pre-market
16 approval application.

17 The next item of business is for us to
18 introduce ourselves, and these panel members are those
19 giving of their time to help the FDA in FDA matters
20 and help the FDA staff here at this table.

21 I would ask each person to introduce
22 themselves stating your specialty, position title,

1 institution, and your status on the panel as a voting
2 member, industry or consumer rep., et cetera, or as a
3 deputized voting member.

4 Let's start with Dr. Roy.

5 DR. ROY: I'm Subir Roy, Professor, OB-GYN
6 at the Keck School of Medicine, which is the new name
7 for the USC School of Medicine, University of Southern
8 California. I'm a reproductive endocrinologist, and
9 I'm an invited voting member of the panel.

10 DR. McCAULEY: Rob McCauley, Professor of
11 Surgery and Pediatrics, University of Texas Medical
12 Branch, and Chief of Plastic Surgery at the Shriners
13 Burns Hospital. I'm a plastic surgeon, voting member.

14 DR. TALAMINI: Mark Talamini, Associate
15 Professor of Surgery at Johns Hopkins University
16 School of Medicine, and I'm a deputized voting member.

17 DR. DeMETS: I'm Dave DeMets, a
18 biostatistician from the University of Wisconsin in
19 Madison, and I'm professor and chair of the
20 department. My specialty is biostatistics, especially
21 those related to clinical trials.

22 MS. BRINKMAN: I'm Maxine Brinkman,

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1 Director of Women's Services, Mercy Medical Center,
2 North Iowa, and I represent the Department of Consumer
3 Affairs.

4 DR. YAROSS: Marcia Yaross, Director of
5 Regulatory Affairs at Allergan, Irvine, California,
6 and I am the industry representative for this
7 morning's meeting.

8 MR. DILLARD: Jim Dillard. I'm the Acting
9 Director of the Division of General and Restorative
10 Devices here at FDA, and my background is in
11 biomedical engineering.

12 DR. DAVIS: Mary Davis. I'm a professor
13 of pharmacology and toxicology at West Virginia
14 University. My specialty is in toxicology, and I'm a
15 deputized member.

16 DR. EDMISTON: Charles Edmiston, Associate
17 Professor of Surgery and hospital epidemiologist in
18 Medical College of Wisconsin. My specialty is
19 surgical microbiology, and I'm a deputized member of
20 this panel.

21 DR. LEVY: I'm Barbara Levy. I'm a
22 clinical gynecologist and clinical assistant professor

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1 of OB-GYN at the University of Washington and at Yale
2 University School of Medicine. I've been a consultant
3 to the OB-GYN Devices Panel for many years, and I'm a
4 deputized voting member.

5 DR. KRAUSE: I'm David Krause, and I've
6 already introduced myself.

7 CHAIRMAN WHALEN: Thank you.

8 I'd like to note for the record that the
9 voting members present constitute a quorum as required
10 by 21 Code of Federal Regulations, Part 14.

11 To begin, we're going to hear from Mr.
12 Stephen Rhodes, who will give the panel an update
13 since our last meeting in June of 1999.

14 Mr. Rhodes.

15 MR. RHODES: Thank you, Dr. Whalen.

16 Good morning, and welcome to everyone. I
17 am the Branch Chief of the Plastic and Reconstructive
18 Surgery Devices Branch, one of the two branches under
19 the purview of this panel, and I will be giving an
20 update on activities since the last panel meeting in
21 these two branches.

22 This panel last met in June of last year

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1 to discuss Intuitive Surgical's endoscopic surgical
2 control system. Since that time, FDA has been working
3 with Intuitive Surgical to bring closure to that
4 application.

5 In plastic surgery, we published a final
6 rule in August 19th, requiring the submission of
7 saline filled breast implant PMAs within 90 days.

8 On October 5th, we released for public
9 comment a draft guidance on preclinical and clinical
10 data and labeling for breast prostheses. This
11 guidance unifies three separate old, existing
12 guidances for saline filled, gel filled, and
13 alternative filled breast implants, and provides more
14 information on clinical studies and updates, the kind
15 of data that we want to see in breast implant PMAs.

16 The official comment period for this
17 guidance ended January 5th. However, we are always
18 interested in receiving comments on this guidance and
19 any guidance.

20 On November 4th, four types of wound
21 dressings were classified as Class 1 devices, exempt
22 from pre-market notification. This panel recommended

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1 that these dressings be classified as Class 1 exempt
2 devices at its November 17th, 1998 meeting.

3 The four types of dressings are non-
4 resorbable gauze/sponge for external use, hydrophilic
5 wound dressing, occlusive wound dressing, and hydrogel
6 wound dressing. The classification does not include
7 dressings that contain drugs, such as antimicrobial
8 agents, added biologics such as growth factors, or as
9 composed of materials derived from animal sources.

10 Working with the OB-GYN Branch, we have
11 just released for public comment a draft guidance for
12 resorbable adhesion barrier devices for use in
13 abdominal and/or pelvic surgery. This guidance will
14 be discussed at the OB-GYN panel meeting scheduled for
15 the 25th of this month. Some members of this panel
16 will be joining the OB-GYN panel to discuss this
17 guidance because of the overlap with adhesion barrier
18 products between these two branches.

19 Lastly, the next meeting of the General
20 and Plastic Surgery Panel is scheduled for March 1st,
21 2nd, and 3rd.

22 Thank you again for your participation in

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1 today's meeting.

2 CHAIRMAN WHALEN: Thank you, Mr. Rhodes.

3 We are now going to proceed into the open
4 public hearing session of the meeting. Anyone who is
5 going to be addressing the meeting during this and all
6 subsequent sessions is asked to speak clearly into the
7 microphone as the transcriptionist is dependent upon
8 this means to provide an accurate record of the
9 meeting.

10 We are requesting that anyone who makes
11 statements during this open public hearing session of
12 the meeting disclose whether they have financial
13 interests in any medical device company.

14 Before making your presentation to the
15 panel, in addition to stating your name and
16 affiliation, please state the nature of your financial
17 interest, if any.

18 We have had no formal requests of anyone
19 to speak at this time. So I would ask if there is
20 anyone who wishes to address the panel in this public
21 hearing session please raise your hand to identify
22 yourself.

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1 (No response.)

2 CHAIRMAN WHALEN: Since there are no
3 requests to speak in the open public hearing, we can
4 now proceed to the open committee discussion.

5 I would like to remind public observers at
6 this meeting that while this portion of the meeting is
7 open to public observation, public attendees may not
8 participate except at the specific request of the
9 panel.

10 However, there will be a further
11 opportunity later in the day for the public to
12 comment.

13 We are now then ready to begin with the
14 sponsor's presentation.

15 MS. KEYPORT: Good morning, Dr. Whalen and
16 members of the Advisory Panel. I'm Georgiann Keyport,
17 Director of Regulatory and Clinical Affairs at
18 Lifecore Biomedical.

19 On behalf of the INTERGEL team, I'd like
20 to begin by thanking the members of the FDA review
21 team for their diligent work and thorough reviews
22 during the course of this project.

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1 We'd also like to thank you members of the
2 advisory panel for your time in preparing for and
3 participating in this meeting today. We welcome the
4 opportunity to review our pre-market approval
5 application for the Devices Panel.

6 By way of background, Lifecore Biomedical
7 is a device company located near Minneapolis,
8 Minnesota. We have been involved in the development
9 and manufacture of hyaluronic based products for over
10 17 years.

11 INTERGEL Adhesion Prevention Solution,
12 previously known as Lubriccoat gel, was initially
13 developed by Ethicon and subsequently transferred to
14 Lifecore where the final development work and
15 manufacturing scale-up were completed.

16 INTERGEL Solution has been approved for
17 sale in Europe, Canada, and South Africa, and we are
18 now seeking approval in the U.S.

19 And I'd like to introduce the speakers on
20 the presenter agenda for today. Dr. Douglas Johns
21 from Ethicon is a consulting scientist to Lifecore
22 Biomedical and has been primarily responsible for the

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1 development of INTERGEL solution. He has served as
2 the project manager for Lifecore for this project and
3 has been involved in all aspects of the clinical
4 trial.

5 Dr. Johns will present the results of the
6 randomized clinical study.

7 Dr. Gere diZerega, Professor of Obstetrics
8 and Gynecology at Women's Hospital, L.A. County, and
9 University of Southern California Medical Center, he's
10 served as the medical review officer in this study.

11 Dr. diZerega will present the safety
12 profile of INTERGEL Solution and provide a clinical
13 perspective.

14 Additionally, we have a number of other
15 individuals available to address any questions you may
16 have. We have Dr. Fred Hoeler, our statistician; Dr.
17 Alan Johns and Dr. Melvin Thornton, who were principal
18 investigators in this study; and finally, Dr. John
19 Dooley and Dr. Kathy Rodgers, who are the
20 toxicologists who performed the INTERGEL preclinical
21 animal studies.

22 We expect our presentation to take about

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1 45 minutes. We'd like to ask to hold questions until
2 the end, as there should be ample time to do that. So
3 unless there are any questions at this point, we will
4 begin.

5 DR. JOHNS: Thank you, Georgiann.

6 Members of the panel, Food and Drug
7 Administration, thank you for the opportunity to
8 present to you the data supporting the pre-market
9 approval application for Lifecore Biomedical's
10 INTERGEL Adhesion Prevention Solution.

11 INTERGEL is a sterile, nonpyrogenic, amber
12 colored, viscous solution of hyaluronic acid, which
13 has been cross-lined by ferric ions and adjusted to
14 isotonicity with sodium chloride.

15 Hyaluronic acid, the principal component
16 of the device, is a naturally occurring polysaccharide
17 which is present in all vertebrates with high
18 concentrations in female reproductive tissue, synovial
19 fluid, and the vitreous of the eye.

20 HA has been in approved medical devices in
21 the United States since 1981, and INTERGEL has been
22 marketed under a CE mark in Europe since June of '98.

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1 INTERGEL is packaged in a 300 milliliter,
2 bellow type bottle with an extension tube which is
3 provided sterile in a plastic tray with a Tyvek lid.

4 As Georgiann mentioned, the name
5 "INTERGEL" was selected for commercial distribution.
6 Previously the product was referred to as Lubriccoat
7 0.5% ferric hyaluronate gel. They are, in fact, one
8 and the same.

9 The ionic cross-linking with iron
10 increases the viscosity of the hyaluronic acid and
11 increases the interperitoneal residence time relative
12 to HA which results in superior efficacy, which has
13 been demonstrated in numerous preclinical models.

14 This superior efficacy has also been
15 demonstrated in the clinical studies we will be
16 discussing today. These studies demonstrate that
17 INTERGEL is effective in reducing the incidence,
18 extent and severity of post surgical adhesions
19 throughout the abdominal cavity following gynecologic
20 surgery.

21 It's effective in reducing all types of
22 adhesions, including reformed adhesions, adhesions at

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1 surgical sites, and de novo adhesions. This effect is
2 throughout the abdominal cavity and not restricted to
3 a single site of placement as with the solid barrier
4 products.

5 Prior to initiation of clinical studies,
6 INTERGEL was evaluated in numerous preclinical models
7 to optimize the formulation, and a battery of safety
8 and related studies were carried out. INTERGEL was
9 evaluated then in a single center, open label pilot
10 study in female patients undergoing peritoneal cavity
11 surgery by a laparotomy with a planned second look
12 laparoscopy.

13 Patients received either 300 milliliters
14 of INTERGEL or lactated Ringer's solution just prior
15 to closure. A total of 23 patients were enrolled in
16 this pilot study, 13 treatment and ten control.

17 The safety profile of INTERGEL was found
18 to be comparable to lactated Ringer's. There were no
19 clinically significant differences in serum chemistry
20 nor hematology, and there was no serious adverse
21 events in the study.

22 INTERGEL also significantly reduced

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1 adhesions in the pilot study.

2 Following the pilot study, a pivotal
3 multi-center study was initiated to assess the safety
4 and efficacy of INTERGEL in reducing adhesions in
5 patients undergoing peritoneal cavity surgery.

6 This study was a third party blinded,
7 parallel group, controlled, randomized design in which
8 female patients undergoing conservative surgery by way
9 of laparotomy for the planned second look laparoscopy
10 received either 300 milliliters of INTERGEL or
11 lactated Ringer's at the completion of the surgical
12 procedure just prior to closure.

13 This study was carried out in 11 centers
14 in the U.S. and five centers in Europe.

15 Patients meeting the inclusion and
16 preoperative exclusion criteria were scheduled for
17 surgery. On the day of surgery patients were assigned
18 the next available study number and a sealed carton
19 containing study material was transferred to the
20 operating room.

21 During the surgery a standard list of
22 interoperative exclusions was assessed to insure

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1 patient qualification prior to opening of the sealed
2 carton.

3 The interoperative assessment included
4 evaluation of adhesions at 24 specific anatomical
5 sites, including sites in the pelvis and sites
6 throughout the abdomen. Patients with adhesions to
7 more than 11 of these sites were to be excluded from
8 the study as were patients who had any of these sites
9 removed during the surgical procedure.

10 Those patients meeting the study criteria
11 were enrolled in the study, and the study material,
12 either INTERGEL or lactated Ringer's, was instilled
13 into the peritoneal cavity at the conclusion of the
14 surgery.

15 Blinding was maintained by one two
16 methods. In the first method study materials were
17 removed from the sealed carton and applied by a
18 surgical assistant after the primary surgeon had left
19 the operating room, enabling the primary surgeon to
20 then conduct the second look laparoscopy.

21 Alternatively, the initial surgery and
22 second look were carried out by different surgeons if

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1 the primary surgeon instilled the study material.

2 Installation of the product following a
3 laparotomy procedure is shown in the following video
4 clip, we hope. Come on. There we go.

5 The product is transferred to the sterile
6 field. The tab is removed simply by twisting. The
7 extension tube is attached, and then the gel is
8 instilled directly into the peritoneal cavity by
9 simply compressing the container.

10 All 300 milliliters of the product is
11 instilled.

12 Okay. Concomitant medications and adverse
13 events are monitored throughout the postoperative
14 period. Laboratory evaluations and abdominal
15 auscultation and percussion are carried out at day
16 three or prior to discharge and at a follow-up visit
17 between day seven and day 28 following surgery.

18 Additional blood work is done just prior
19 to the second look laparoscopy, which is targeted for
20 six to 12 weeks after the initial operation at which
21 time adhesions are again assessed at each of the 24
22 anatomical sites.

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1 The primary efficacy variable is an
2 adhesion score using the adhesion scoring method of
3 the American Fertility Society applied to 24
4 anatomical sites. We've termed this the modified AFS
5 score.

6 To fully understand the modified AFS
7 score, I think it's best to step back and look at the
8 actual AFS score from which it was derived. The
9 American Fertility Society recognized a need for a
10 standard classification scheme for mechanical problems
11 associated with infertility, and in 1988, the AFS
12 formed a subcommittee to establish a scoring system
13 for adnexal adhesions which was easy to use and
14 related to the patient's prognosis for conception.

15 It is now the most widely used scoring
16 system for adhesions, and it has been validated by
17 correlation with clinical outcomes, such as pain and
18 fertility through published literature.

19 The AFS system is a scoring system which
20 takes into account only adnexal adhesions. Thus,
21 adhesions to each tube and each ovary are assessed.
22 For instance, for the right ovary if an adhesion is

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1 present, it's determined whether it is filmy or dense.

2 If the adhesion is filmy and covers less
3 than one third of the ovary, it's assigned a score of
4 one. If it encloses between one third and two thirds
5 of the ovary, it's assigned a score of two, and if the
6 enclosure is greater than two thirds, it's assigned a
7 score of four.

8 On the other hand, if an adhesion is
9 dense, the scores are assigned as four, eight, and 16.
10 The same procedure is followed then for the right
11 tube, the left ovary, and the left tube.

12 A score is then obtained by summing up the
13 total for the right ovary and right tube and for the
14 left ovary and left tube. The score for the right
15 adnexa and the score of the left adnexa, which is
16 lower, is then used as a basis for prognosis.

17 The modified AFS score is derived in a
18 similar manner, except instead of the right ovary,
19 tube, and so on, each of the 24 anatomical sites I
20 mentioned is assigned a score in the same fashion. So
21 a score for each of the 24 anatomical sites could
22 range from zero to 16. These are added up and

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1 averaged then for each patient.

2 In addition to the modified AFS score,
3 secondary efficacy variables included the proportion
4 of sites with adhesions. The proportion is defined as
5 the number of sites with adhesions divided by the
6 number of possible sites.

7 Severity of adhesions is also determined.
8 This is a mean score for 24 sites where no adhesion is
9 given a score of zero. A mild adhesion is given a
10 score of one, and a severe adhesion is given a score
11 of three.

12 Extent of adhesions is also determined.
13 Again, it's a mean score for the 24 sites, this time
14 on a four point scale, none equaling zero, localized
15 adhesions given the score of one, moderate a score of
16 two, and extensive a score of three.

17 And what you can't see at the bottom, I
18 believe, is the AFS. That's the best we can do?
19 Okay.

20 Efficacy was evaluated at each of those 24
21 anatomical sites together, as well as for a pelvic
22 site grouping and abdominal site grouping. Each

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1 individual site, sites with endometriosis were
2 assessed, as were sites with sutures. The method of
3 adhesiolysis was also analyzed, and analysis was also
4 carried out by surgical procedure, the latter being in
5 addition to the protocol.

6 Adhesions were also categorized looking at
7 all adhesions together, as well as reformed adhesions,
8 which of course are adhesions which occur at sites
9 where an adhesion was present at baseline and lysed.

10 De novo adhesions are adhesions which form
11 at sites which had no adhesion at the first procedure.
12 These can either form at surgical sites or at
13 nonsurgical sites.

14 And we also had a surgical site adhesion
15 grouping which includes reformed adhesions and de novo
16 adhesions at surgical sites.

17 There were a total of 303 patients
18 randomized in the study. Of these, 281 were treated.
19 That is, they received either INTERGEL or lactated
20 Ringer's solution. Two hundred and sixty-five of the
21 281 completed the study. That is, they had a second
22 look laparoscopy.

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1 One hundred and seventy-seven of these
2 patients were from the United States, or roughly two
3 thirds, and one third were from the European centers.

4 The 281 patients, all those that received
5 the study material, were assessed for safety while the
6 265 patients who completed the second look were
7 evaluable for efficacy.

8 An intent to treat analysis was carried
9 out on the 281 patients, which includes the 16
10 patients who did not return for second look, but
11 first, I will focus on the results looking at the
12 evaluable population or this 265 patients for whom we
13 have data.

14 Myomectomy was the most common procedure
15 performed. Approximately 70 percent of the patients
16 underwent a myomectomy procedure. Adhesiolysis,
17 ovarian procedures, and tubal procedures were also
18 fairly common. And surgical treatment of
19 endometriosis was also carried out, although on a
20 small number of patients.

21 The baselines prior to any surgical
22 intervention were similar between the two groups. The

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1 modified AFS score was similar. The number of
2 adhesions, the proportion, extent, and severity were
3 all similar between treatment and control group.

4 The amount of surgical intervention,
5 including the number of adhesions which was lysed, and
6 the number of surgical sites were also similar, and as
7 a result not surprisingly, the post surgical baseline
8 or the number of adhesions left behind were also
9 similar between the two groups.

10 While the baselines were similar, INTERGEL
11 significantly reduced adhesions at second look. This
12 reduction amounts to about a 45 percent reduction in
13 the modified AFS score.

14 Now, the modified AFS score, the results
15 shown for you here, takes into account, as I
16 mentioned, the proportion, extent, and severity of
17 adhesions at all 24 anatomical sites, but as you can
18 see, the proportion, the extent, and the severity were
19 also significantly reduced.

20 This amounts to about a 17 percent
21 reduction in the proportion, 27 percent in extent, and
22 31 percent in severity.

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1 The reduction in adhesions was observed
2 for all adhesion types as well. A 40 to 50 percent
3 reduction in the modified AFS score was observed for
4 reformed adhesions. De novo adhesions, this includes
5 both non-surgical and surgical site de novo adhesions,
6 as well as adhesions at all surgical sites.

7 Analysis by surgical procedure was also
8 carried out. Again INTERGEL reduced the modified AFS
9 score from between 30 and 60 percent for all the
10 procedures. As you can see it's patients undergoing
11 myomectomy, adhesiolysis, ovarian procedures were
12 grouped together, as was tubal procedures, and you can
13 see ablation of endometriosis as well.

14 INTERGEL consistently reduced adhesions at
15 all anatomical sites, including both the pelvic sites
16 and the abdominal sites. The circles in this plot,
17 positive mean values, depict a positive treatment
18 effect for each of the anatomical sites. So anywhere
19 the circle is positive is a positive effect for
20 INTERGEL.

21 The lines are the 95 percent confidence
22 intervals. Anywhere the line is above zero would mean

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1 a significant effect, and as you can see, 12 of --
2 well, there's a couple of lines missing there. They
3 are on my screen, but 12 of the 24 sites reached
4 statistical significance.

5 For example, you can see the left and
6 right cephalad anterior peritoneum, the anterior
7 peritoneum incision, the small bowel, and so on, and
8 you can see the sites which actually reached
9 significance.

10 INTERGEL also reduced adhesions in the
11 U.S. and European populations. As shown in this
12 slide, you can see the baseline adhesions were similar
13 between INTERGEL and control, and at second look,
14 there's a significant reduction in the number of
15 adhesions. The P value is .003.

16 Similarly, there's a reduction in the
17 number in the modified AFS score at second look for
18 the European population, a P value of .026, and there
19 was no difference in the groups at baseline in Europe.

20 The results amount to about a 43 and a 49
21 percent reduction in the scores, respectively,
22 although you can see that the baseline values in

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1 Europe and the U.S. were different.

2 These baseline differences are really a
3 reflection of the surgical procedures that were
4 performed. In the United States, approximately 80
5 percent of the patients underwent a myomectomy
6 procedure and 40 percent underwent adhesiolysis, and
7 in Europe it was the opposite. Approximately 40
8 percent were myomectomy, and about 80 percent were
9 adhesiolysis patients.

10 The patients undergoing myomectomy
11 procedures, in general, had few adhesions at baseline,
12 and that was true in the U.S. and in Europe, and
13 produced more adhesions at second look.

14 However, in both cases, as you can see,
15 INTERGEL significantly reduced adhesions in the United
16 States. The reduction was quite large in Europe,
17 although the value did not reach statistical
18 significance.

19 Adhesiolysis patients, on the other hand,
20 start with more adhesions at baseline, but again,
21 INTERGEL significantly reduces adhesions at second
22 look in both the U.S. and European populations.

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1 All of these treatment group comparisons
2 presented so far were performed using student's T
3 tests. We also did overall analyses using factorial
4 analysis of covariance.

5 This was done for both the evaluable
6 population and the intent to treat population, as
7 specified in the protocol.

8 In the ANCOVA analyses, treatment group
9 and center were included as categorical variables, and
10 baseline modified AFS score was included as a
11 continuous covariate to adjust for the initial
12 baseline differences.

13 The overall effect of treatment was found
14 to be statistically significant, as was the effect of
15 baseline level, the latter indicating, of course, if
16 you start with fewer adhesions, you'll end up with
17 fewer adhesions or vice versa.

18 The overall effect was significant. The
19 center effect approached significance, but the
20 treatment by center interaction remained
21 nonsignificant, indicating that the data sets are
22 poolable.

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1 Examination of the least squares means
2 data from this ANCOVA analysis indicated an INTERGEL
3 solution had fewer adhesions than the lactated
4 Ringer's solution group in all but one of the centers.
5 In this bubble diagram, values above the zero axis
6 indicate a positive effect for INTERGEL, and the size
7 of the bubble is proportional to the number of
8 patients that was enrolled.

9 Although some centers have higher overall
10 adhesion values than others, INTERGEL reduced
11 adhesions in all but one center.

12 As I mentioned, an intent to treat
13 analysis was performed in which treated patients who
14 did not receive a second look laparoscopy were defined
15 as treatment failures and given the worst possible
16 second look modified AFS score of 16. Because of the
17 extreme skewness produced by adding in patients with
18 the worst possible score, analysis of variance was
19 performed after rank transformation of the data as
20 stated in the protocol, and the results were found to
21 be very similar for the intent to treat rank
22 transformed as the evaluable.

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1 The overall treatment effect was
2 significant. The baseline level was still
3 significant. The center effect approached
4 significance as before, but the treatment by center
5 interaction remained nonsignificant.

6 The list of patients who discontinued from
7 the study and the reason for their discontinuation is
8 summarized for you here. One patient became pregnant
9 in the treatment group. One had a failed laparoscopy
10 due to obesity, and six treatment and one control
11 patient were feeling fine and simply did not want to
12 have another surgery.

13 There was one treatment patient lost to
14 follow-up and three patients in each group who had
15 some complaints, but simply did not want a second look
16 laparoscopy.

17 While the overall effect of treatment was
18 retained with the rank transformed data, despite the
19 imbalance of patients who discontinued from the study,
20 12 INTERGEL and four control, it's important to note
21 that we believe that additional intent to treat
22 analyses on subgroups is not appropriate. It is

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1 clinically inconsistent to assign the worst possible
2 score to patients who become pregnant or simply did
3 not want a second look laparoscopy because of their
4 well-being.

5 The analysis we presented here on the
6 evaluable population includes all of the data. No
7 data from any patient is excluded. The intent to
8 treat analyses create artificially created data which
9 masks the ability to determine the device
10 effectiveness.

11 Examination of adnexal adhesions by way of
12 the standard AFS score, again, shows a significant
13 effect of INTERGEL. As you can see, at baseline the
14 standard AFS score now for just the ovaries and tubes
15 is similar at baseline, and at second look is
16 statistically significant. The P value is .001.

17 This amounts to about a 61 percent
18 reduction in the AFS score.

19 Now, these averaging techniques can be
20 used to compare treatment and control reduction.
21 Percentage reduction in these mean scores however is
22 difficult to interpret, and they tend to obscure

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1 individual patient benefit.

2 Individual patient results can be
3 ascertained by evaluating the number of patients in
4 each group who shift from one AFS category to another.
5 The AFS prognostic classifications are shown for you
6 here. Patients who have AFS scores between zero and
7 five are considered to be minimal, six to ten mild, 11
8 to 20 moderate, and 21 to 32 severe.

9 As you can see, in the INTERGEL solution
10 group, 109 patients started in the minimal category.
11 Of these 109, 103 remained minimal. Four became mild.
12 One each became moderate and severe.

13 In contrast, 109 patients in the control
14 population stated in the minimal category, 96 remained
15 minimal, six became mild, three became moderate, and
16 four became severe.

17 Overall you can see that there are more
18 patients in the minimal category than in the treatment
19 group, than in control, and there are fewer patients
20 in the mild, moderate, and severe category than in the
21 control population.

22 Analysis using the Cochran Mantel Haenscel

1 Test controlling for baseline level indicates a highly
2 significant P value, which you can't see. It's
3 actually .001.

4 As I mentioned earlier, several
5 investigators have evaluated pain and fertility in
6 relation to the patient's AFS score and, in general,
7 have concluded that the minimal and mild AFS category
8 tend not to be problematic while the moderate and
9 severe categories tend to be.

10 Combining these groups in what we have
11 termed a binary analysis indicates a highly
12 significant result. The P value here is actually
13 .003. As you can see, of the 122 patients who started
14 in the minimal and mild category, only three became
15 moderate and severe. In contrast, ten of the 117
16 control patients became moderate and severe.

17 All nine of the patients who started out
18 in the moderate and severe category in the INTERGEL
19 group moved to the minimal and mild, and in the
20 control population, only about half, ten of the 17,
21 moved.

22 Overall you can see that there are only

1 three patients in the moderate and severe category
2 versus 17 in the control population.

3 Now, a similar analysis can be done using
4 the modified AFS score that's shown for you here. As
5 you can see, there were 19 patients in the INTERGEL
6 group who remained totally adhesion free. You can't
7 see the sum here, but the total is 12 in the control
8 population.

9 There were also 18 patients in the
10 moderate classification for the INTERGEL group or --
11 excuse me -- for the control population and eight in
12 the INTERGEL group. There were six severe patients in
13 the control population and none in the severe
14 population who have received INTERGEL.

15 In the binary analysis, again, you can see
16 these numbers. There are actually three times as
17 many, eight versus 24, patients who end up with
18 moderate versus severe -- moderate and severe
19 adhesions in the control population compared to the
20 INTERGEL population.

21 Now, this result is also reflected in an
22 analysis looking at the total number of anatomical

1 sites which received each of the possible modified AFS
2 score. Recall for each site it can have zero if
3 there's no adhesion, a one, two, four, eight or 16
4 value.

5 What this slide shows you is there were
6 approximately 200 more anatomical sites that received
7 a score of zero or one in the INTERGEL group, and
8 there were approximately 200 more anatomical sites in
9 the control population that received a score of eight
10 or 16. The scores of eight or 16 can only come from
11 moderate or extensive, severe adhesions.

12 In summary, INTERGEL solution was shown to
13 reduce the incidence, extent, and severity of
14 adhesions compared to lactated Ringer's solution. The
15 mean modified AFS score was reduced by 44 percent.
16 The AFS score was reduced by 61 percent. The
17 proportion, severity, and extent of post surgical
18 adhesions were reduced.

19 De novo, reformed, and surgical site
20 adhesions were reduced. The reduction was consistent
21 for sites throughout the abdomen. The reduction was
22 observed for all surgical procedures, and it was

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1 observed for both the U.S. population and the European
2 population.

3 Analysis of the individual patient
4 outcomes readily demonstrates the clinical utility of
5 the product. More INTERGEL solution treated patients
6 were totally adhesion free, 19 versus 12. Fewer
7 INTERGEL solution treated patients had a moderate or
8 severe outcome, regardless of the scoring system, and
9 fewer INTERGEL solution treated patients had a severe
10 outcome.

11 And now Dr. diZerega will review the
12 safety results for INTERGEL.

13 DR. diZEREKA: Thank you, Dr. Johns.

14 Members of the panel, I would like briefly
15 to highlight the results of the safety assessments.
16 My presentation is divided into four sections:
17 adverse events, postoperative, pre and postoperative
18 laboratory test evaluations, concomitant medications,
19 and gross observations seen at the time of second look
20 laparoscopy.

21 This slide lists the adverse events which
22 occurred in at least five percent of the patients. On

1 the left-hand column are the body systems, followed by
2 the incidence of occurrence in the patients who
3 received INTERGEL solution and lactated Ringer's
4 solution. The only body system where a significant
5 difference occurred was listed as allergic reaction,
6 where control patients had a higher incidence than
7 treated patients.

8 Of interest, there were no significant
9 differences in pain, fever, incisional problems, or
10 constipation.

11 This slide summarizes adverse events for
12 the two groups. Once again, there were no significant
13 differences in the frequency of assignment of the
14 adverse events between the INTERGEL group and the
15 control group. For the SAEs, eight for the treatment,
16 seven for the control.

17 As regards the laboratory test results,
18 there were no significant differences prior to
19 surgery. This slide summarizes the postoperative lab
20 results on day three after surgery.

21 Although there were no significant
22 differences in kidney and liver function tests, there

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1 were statistically significant differences in the
2 white blood cell count which were due to a relative
3 elevation in polymorphonuclear cells shown on the
4 disappearing bottom portion of your slide.

5 The WBC level for the INTERGEL treated
6 patients was 8.9 thousand and for the control patients
7 7.9 thousand, both values certainly well within the
8 limits of normal for three days postoperative. This
9 statistical difference was no longer apparent at days
10 seven to 28, nor at the time of second look
11 laparoscopy.

12 In summary then, no differences in adverse
13 events, concomitant medications, or laboratory values
14 were noted, except for the white blood cell count. We
15 looked carefully for any correlation between these
16 white blood cell counts and clinical findings.

17 No pattern of clinical sequelae, including
18 infection and interperitoneal adhesions was identified
19 in patients with elevated WBC levels. Since these
20 findings of a low, transient elevation of white blood
21 cell concentration was not common to any particular
22 center, demographic or clinical manifestation, it was

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1 considered to be a brief sub-clinical response without
2 clinical significance.

3 As regards the visual appearance of the
4 peritoneal cavity at the time of second look
5 laparoscopy, there was no evidence of granulomata nor
6 foreign body reaction.

7 Some patients contained evidence of
8 peritoneal discoloration due to the trauma of surgery
9 or residual hyaluronic acid. These discolorations
10 were often difficult to distinguish from hemosiderin
11 or peritoneal clot.

12 INTERGEL solution, shown to reduce the
13 incidence, extent, and severity of adhesions following
14 gynecological surgery. What types of adhesions was
15 INTERGEL effective in reducing? It was all types,
16 reformed adhesions, surgical site adhesions, and de
17 novo adhesions.

18 Where did INTERGEL work? It worked
19 broadly. It was effective throughout the abdominal
20 cavity.

21 Was INTERGEL safe? The safety profile was
22 comparable to that of lactated Ringer's.

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1 In summary, the analysis of individual
2 patient outcomes readily demonstrates the clinical
3 utility of INTERGEL solution. More INTERGEL solution
4 treated patients were totally adhesion free. Fewer
5 INTERGEL treated patients had a moderate or severe
6 outcome, and fewer INTERGEL solution treated patients
7 had severe outcomes.

8 The FDA has raised questions about the
9 poolability of data from this study. No study is
10 perfect. This is a prospective, randomized, blinded,
11 controlled clinical trial. In such a study, we cannot
12 evaluate the data until the study is completed. This
13 study is a good one with good results. By chance,
14 some of the baseline data are not the same between
15 centers, but the response to treatment is consistent
16 across centers.

17 In conclusion, the data from this study
18 provides valid, scientific evidence in support of the
19 safe and effective use of INTERGEL adhesion prevention
20 solution as a single use intraperitoneal instillate
21 for the reduction of adhesions following gynecological
22 surgery.

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1 Now, before I close, I would like to
2 address the clinical significance of all the data
3 provided to you in the panel pack, including the
4 representative samples Dr. Johns and I have presented
5 to you this morning.

6 Clinical significance? Two questions.
7 What do these results mean to a practicing surgeon,
8 and how does INTERGEL help patients?

9 Yes, it is important that there was a 60
10 percent increase in the number of patients who were
11 adhesion free if they had received INTERGEL.

12 Yes, it is important that if a patient had
13 no adhesions at the time of surgery, that patient was
14 twice as likely not to develop overwhelming adhesive
15 disease after surgery if they had received INTERGEL
16 solution.

17 Yes, it is important that the incidence,
18 the incidence of the most clinically significant
19 adhesion, the so-called surgical site adhesion, the
20 adhesion that forms at our primary site of surgery and
21 in so doing limits the effectiveness of our surgical
22 procedures, the incidence of the surgical site

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1 adhesion was also reduced if the patient received
2 INTERGEL solution.

3 And, yes, that difference was also
4 statistically significant.

5 Perhaps most importantly, INTERGEL helps
6 patients. INTERGEL helps patients by reducing the
7 chance of failed surgical therapy from postoperative
8 adhesions. As shown by both comprehensive scoring
9 systems, the AFS and the modified AFS, control
10 patients were three to five times more likely to have
11 a bad outcome than patients who received INTERGEL
12 solution, 17 to three, 24 to eight.

13 In other words, the use of INTERGEL
14 solution reduced by 80 percent the change of a patient
15 developing widespread adhesive disease.

16 To finish, each year many of our patients
17 undergo operative procedures in the hopes that these
18 patients will benefit in clinical outcome as a result
19 of that surgery. In this PMA, clear evidence has been
20 provided that INTERGEL solution provides the surgeon
21 with further assurance that such procedures will
22 actually benefit our patients.

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1 Thank you for your attention.

2 MS. KEYPORT: We would be very happy to
3 entertain questions.

4 CHAIRMAN WHALEN: And, indeed, at this
5 time it is appropriate for any panel member wishing to
6 either ask questions or express opinions about the
7 sponsor's presentation to do so.

8 Dr. DeMets, would you have any questions
9 at this time to start off?

10 DR. DeMETS: Yes, actually for either of
11 the presenters or perhaps the statistician. I'm
12 trying to understand this AFS score, the modified AF
13 -- AMS score. The scores themselves were zero, two,
14 four, eight, 16 as I recall. I assume that if you get
15 a 16 you're twice as bad as if you get a score of
16 eight, or is it just a ranking?

17 Does it say one is worse than the other or
18 does it really say one is twice as bad? That's what
19 I'm trying to understand.

20 DR. diZEREKA: Thank you for your
21 question.

22 I think the answer is in a different

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1 direction. The difficult that we've all had over the
2 20 years that I've been involved with adhesion
3 prevention research is trying to find a way to make
4 clinical sense out of these observations that
5 withstand numerical evaluation.

6 Years ago we used to actually identify the
7 incidence and think that was the important parameter,
8 and we found in our surgical practice that, in fact,
9 it was very different. One single, small film
10 adhesion was a different surgical procedure than
11 large, extensive, vascularized adhesions.

12 And so in a way to try to address this, in
13 1988 the AFS, the American Fertility Society, came up
14 with this scoring system, and the idea was to provide
15 a prognostic indicator of the likely outcome of the
16 patient, and the way it actually turned out with the
17 patients with the moderate and severe scores were very
18 unlikely to conceive whereas the patients with the
19 lower scores had a much greater chance of conception.

20 That gave us then a tool to talk to the
21 patient's husband when we came out of the operating
22 room in terms of what they were likely to expect. So

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1 it's not a matter of is eight twice as great as 16.
2 It's more a matter of categorizing the patient into
3 those categories and then expressing that as a
4 prognostic indicator for clinical benefit.

5 DR. DeMETS: I appreciate the answer. If
6 what you say is the case, the reason it matters to me
7 is that the analysis that you have done depends on
8 whether eight is twice as four and 16 is twice as bad
9 as eight or it's a ranking.

10 I understood you to say it really is an
11 ordering system, which is better than the other. So
12 I would, I think interpret your answer to suggest that
13 perhaps a ranking analysis of the data would be more
14 appropriate than a computing means and standard
15 deviations.

16 MR. HOELER: My name is Fred Hoeler. I'm
17 the statistician, and I don't know if I'm supposed to
18 say that I'm a paid consultant to Lifecore.

19 It's always been clear to me that this is
20 a ratio scale. You look at the way it is structured,
21 from zero, one, two, four, eight, and 16. As it's
22 been used in previous studies means have always been

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1 used. So we think it's reasonable to treat it as a
2 ratio scale.

3 You may disagree with the ratio, but
4 that's clearly what the clinicians intended.

5 CHAIRMAN WHALEN: Dr. Talamini.

6 DR. TALAMINI: Excuse me. I have a few
7 questions, some practical and some not.

8 When the INTERGEL is actually injected
9 into the abdominal-pelvic cavity, do you stir it
10 around at all, or do you just plot it in there and
11 then that's it?

12 DR. diZEREGA: The question relates to the
13 application of the device. By way of history, Dr.
14 Talamini, I was involved with the pilot study that
15 actually developed the techniques for application of
16 the device. So I had personal experience in the very
17 early days of this, and those data as we've indicated
18 have been published.

19 What we've found is that this viscoelastic
20 device in application into the peritoneal cavity tends
21 to adhere to peritoneal surfaces. If you put some on
22 your hand, you'll find actually that it coats your

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1 hand and doesn't fall off unless you actually put a
2 lot of force to it.

3 And as a consequence, what we've found was
4 that we actually had to use the 300 milliliter volume
5 to fill the entire peritoneal cavity, and in so doing
6 virtually all of the surfaces were covered. We did
7 some preclinical studies in rabbits to calculate the
8 appropriate volume to cover the entire peritoneal
9 surfaces of the peritoneal cavity, and that
10 extrapolated out to the 300 milliliters.

11 An interesting aspect of that at least as
12 a preclinical investigator was in the clinical trial
13 the results for the abdominal organs, which
14 intuitively would be anti-gravitationally affected,
15 were some of the more effective sites in terms of
16 device efficacy, indicating that not only the local
17 coverage, but also the interperitoneal circulation as
18 we breathe and as we have gastrointestinal motility
19 also mixes this viscoelastic gel throughout the
20 peritoneal cavity.

21 And so I think it's very easy to apply the
22 device by simply administering it during the time of

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1 the surgical procedure because the patient's own
2 biology or physiology will actually do the job of
3 peritoneal coverage.

4 DR. TALAMINI: And I didn't see in the
5 protocol. Was irrigation before part of the protocol
6 or at the surgeon's discretion or never used?

7 DR. diZEREGA: The irrigation was
8 essentially at the surgeon's discretion. All of the
9 surgeons we met with prior to the initiation of the
10 clinical trial to make sure there was as much as
11 possible similarity in these types of techniques.

12 Certainly there are differences between
13 surgeons, but virtually all of the surgeons did use
14 irrigation, and all of the irrigation was aspirated at
15 the end of the procedure prior to the application of
16 either the device, INTERGEL, or the control, lactated
17 Ringer's solution.

18 DR. TALAMINI: I have a couple of
19 questions both conceptual and practical about safety.
20 As a GI surgeon who sews a lot of bowel, I need some
21 adhesions. I'd be in big trouble if I didn't have
22 things adheese (phonetic) to my anastomoses.

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1 So along with that I guess I would wonder
2 about that aspect of the whole field. I realize in
3 this study there were no open GI tract. There was no
4 open mucosa, but it certainly is a conceptual issue,
5 and along with that, I may have missed it, but I
6 didn't hear you go through this slide that says
7 patients coded as having an infection where the list
8 goes through the INTERGEL solution infections and the
9 control.

10 I realize there wasn't a numerical
11 difference, but I'd be interested in your comments on
12 the qualitative differences in infections on that
13 slide.

14 DR. diZEREGA: So two questions. Let me
15 talk about the infection slide that I didn't address
16 proactively and then get back to the issue of
17 gastrointestinal repair and the effects of adhesion
18 prevention therein.

19 In terms of the infection slide, we
20 decided to leave that out because of interest in time.
21 As you know, there are less than five percent of the
22 patients were coded as infection. The patients that

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1 received fundamental immunotherapy at all in the
2 active group, two of them were treated with either one
3 antibiotic on one course or one patient received two
4 courses of the antibiotic and both did very, very
5 well.

6 The third patient and the physicians
7 actually in the audience whose patient that was was
8 Alan Johns, and I'd like to all Alan Johns up to have
9 him tell you about the third patient very briefly. It
10 was his patient, and it's an interesting observation
11 clinically, and then I'll get back to talking about
12 the gastrointestinal aspects.

13 Dr. Johns.

14 DR. JOHNS: I'm Alan Johns. I am a
15 private practitioner in Fort Worth, Texas, and an
16 investigator for both the laparotomy and the
17 laparoscopy trial for INTERGEL.

18 And the patient that you're talking about
19 was one that had a large fibroid. When we opened her,
20 there was more peritoneal fluid than I would normally
21 see. I didn't think much about it. I just went ahead
22 and did some cultures, and then within a couple of

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1 days I had a positive chlamydia culture on that fluid.

2 So she probably had active chlamydia at --
3 I'm sure she had active chlamydia at the time,
4 although we didn't know that until we got the culture
5 back.

6 Does that answer that question?

7 DR. TALAMINI: Yes. Thank you.

8 DR. diZEREKA: As regards the healing of
9 the gastrointestinal tract, in the preclinical portion
10 of the PMA bursting strengths of the bowel were
11 determined by doing primary excisions and anastomosis,
12 and there were no changes in the bursting strength of
13 the bowel when INTERGEL solution was added into the
14 peritoneal cavity.

15 And as a consequence, there is no reason
16 that we have today to be unusually concerned about
17 anastomotic repairs moving forward.

18 Now, having said that, when we talk about
19 the labeling you'll see that that's not a primary
20 focus of the labeling.

21 DR. TALAMINI: And I just have one other
22 question about efficacy. How -- I'm not sure how to

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1 phrase this, but certainly laparoscopy is different
2 than laparotomy in trying to evaluate 20 sites for
3 adhesions. How exhaustively did you feel your
4 investigators were able to really measure all of these
5 fairly complex aspects through the laparoscope.

6 DR. diZEREKA: A general comment and then
7 some specifics as we tried to think through that
8 challenge. We organized a monitoring system to assure
9 as much as possible that all of the anatomical sites
10 were being seen by the investigators. As we all know,
11 the laparoscopic image is -- can be recorded by video
12 system. That was done in the study, and that gave us
13 a way as best as we could to make sure that when an
14 investigator said there was or wasn't an adhesion on
15 a specific anatomical site, that anatomical site was,
16 in fact, seen during the laparoscopic procedure, and
17 that's an important consideration, I think, in the
18 quality of the study.

19 Now, how did that actually -- how
20 reasonable was that for different anatomical sites?
21 It turned out to be quite different. For the adnexa
22 in gynecological procedures, there's a lot of

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1 attention to the tubes, ovaries, anterior/posterior
2 side of the uterus, lateral pelvic side walls, and
3 rectal sigmoid. That kind of data we could actually
4 -- we asked the investigators to determine the extent
5 of the organ.

6 We, therefore, required them to be able to
7 visualize the entire organ, for example, the ovary,
8 and make an assessment as what percentage of that
9 ovary was covered with an adhesion.

10 Conversely, with the small bowel, take an
11 easy case. It's impossible to see the 30 feet of the
12 small bowel, and so in a situation with a small bowel
13 those kinds of data we did not collect because we
14 didn't think it was reasonable or practical to ask the
15 surgeons to look through 30 feet of bowel to try to
16 find an adhesion.

17 CHAIRMAN WHALEN: Dr. Edmiston.

18 DR. EDMISTON: I'd like to follow up in
19 Dr. Talamini's question concerning infection, and
20 we're discussing this device as a barrier to adhesion,
21 but the question that I have: is this device also a
22 potential barrier to peritoneal defense mechanisms?

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1 For instance, does the device prevent the
2 migration of peritoneal macrophages? Because we know
3 once there is contamination to the peritoneal cavity,
4 those organisms adhere tenaciously to the serosal
5 mesothelium.

6 Those organisms aren't removed by lavage.
7 If they're still there after the device is applied, do
8 you have any information -- and I know you've been
9 involved in animal studies -- that would suggest that
10 those organisms could be resolved from that surface?

11 DR. diZEREKA: What I'd like to do is call
12 Dr. Kathleen Rodgers to talk with you about that. She
13 was involved in the preclinical animal work. She is
14 a toxicologist well known in this area, and she'll
15 address that.

16 DR. RODGERS: I'm sorry, sir. I didn't
17 see who was asking the question.

18 Okay. Your question was microbial
19 organisms adhering to the serosa.

20 DR. EDMISTON: Un-huh.

21 DR. RODGERS: I'm sorry. Kathy Rodgers,
22 University of Southern California. I'm a paid

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1 consultant to Lifecore.

2 What we did do along the way is look at
3 induction of sepsis by administration of bacterial
4 inocula into the abdomen at an LD-10 level, and I
5 think what addresses your concern is the formation of
6 abscesses in the peritoneal cavity after
7 administration of the device.

8 And what we found was -- I can give you
9 the data if you like -- between the control or the
10 Ringer's lactated treated groups, there is reduction
11 with administration of a clinical level of the
12 material in abscess formation, indicating there was
13 not a blockade to the clearance of the bacteria and
14 subsequent abscess formation.

15 DR. EDMISTON: Now, that was the Onderdomk
16 model, right?

17 DR. RODGERS: Yes, sir.

18 DR. EDMISTON: You didn't use that,
19 evaluate that model using a bowel injury model, like
20 cecalagation puncture?

21 DR. RODGERS: No, we didn't use cecal
22 puncture.

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1 DR. EDMISTON: Okay.

2 DR. RODGERS: No, we did not.

3 DR. EDMISTON: So there was no necrotic
4 material in the bowel when you evaluated that model.

5 DR. RODGERS: That's correct.

6 DR. diZEREKA: The cecal puncture model
7 has been evaluated with hyaluronate containing
8 devices. Published information, 0.4 percent -- as you
9 know, this is a 0.5 percent HA containing solution --
10 0.4 percent HA containing solution in a cecal puncture
11 model, in fact, did very well. There was a reduction
12 of abscesses around the area of the cecal puncture in
13 that publication.

14 Those are not our work. We've read of it
15 other places.

16 I think the infection is something that
17 concerns us all. I think our concern is with very
18 broad usage of this product might small incidences of
19 infection become more problematic, and in consultation
20 with the Food and Drug Administration, what we've
21 decided to do was to go back and repeat the Onderdomk
22 model with a much larger number of animals, a

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1 different inoculation dosage, to try to come to grips
2 with what might be or might not be an important
3 problem.

4 But certainly in our clinical trial and in
5 the preclinical work that we did in submission, it was
6 not something that we saw.

7 CHAIRMAN WHALEN: Dr. McCauley.

8 DR. McCAULEY: I have three questions.
9 One actually relates to the AFS scoring system, which
10 is obviously very subjective and kind of reminds me of
11 the Vancouver Scar Scale system that we use in
12 patients in a different population.

13 What I wanted to ask first is related to
14 the scoring in and of itself. How was it defined what
15 adhesions were flimsy and which adhesions were dense?
16 And was there any type of interevaluator reliability
17 in that scoring system?

18 Because that significantly affects the
19 scores and your outcome.

20 DR. dIZEREGA: Yes. I think you're
21 absolutely right. As this art has evolved over the
22 years, I think what we've begun to do is to try to

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1 address that aspect of it more than aspects of
2 incidents.

3 In order to do that, a few years ago at
4 the International Federation of Fertility and
5 Sterility, an expert's panel was put together to
6 actually address the very question that you're asking,
7 and the recommendation -- and this was a worldwide
8 group -- the recommendation of that panel was to
9 consider those types of adhesions that are classified
10 by words as "dense."

11 The best way to distinguish them from the
12 words of "filmy" or "flimsy" is the presence or
13 absence of vascularization if there is any question.
14 In other words, if it's a translucent adhesion that is
15 -- that is flimsy, that clearly would fit very simply
16 into the lesser category. If that adhesion was very
17 thick, cohesive where the tissue surfaces were
18 actually kissing, that would obviously be a dense
19 adhesion.

20 In that gray zone that you're addressing,
21 the recommendation of this panel, and we certainly
22 adopted it was that if there's any evidence at all of

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1 vascularization or if there is any doubt that it might
2 be dense, to up scale or to upgrade the adhesion at a
3 dense adhesion.

4 Now, clinically to me the biggest
5 difference actually is that issue of vascularization
6 and the ability to identify surgical planes and all of
7 that would put the adhesion in the dense category.

8 DR. McCAULEY: So this was followed by all
9 of the surgeons used in this study for evaluating
10 this?

11 DR. diZEREKA: Yes. Yes, Dr. McCauley.
12 What we did, Dr. Johns and I traveled and spoke to all
13 of the surgeons, the principal investigators, and
14 oftentimes some other surgeons that might be involved
15 in the program.

16 We also met along with the Lifecore
17 people, the clinical coordinators that were involved
18 with the collection of this data to try to make sure
19 as best as we possibly could that the same definitions
20 were used for all of these criteria, and the one that
21 you're asking about received, I think, the most clear
22 direction in that if in doubt, it's dense. If it's

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1 vascularized, it's dense. If it's anything but
2 flimsy, it's dense.

3 DR. McCAULEY: My second question relates
4 to the fact that 70 percent of the patients underwent
5 myomectomies; is that correct in your study?

6 DR. diZEREKA: Yes.

7 DR. McCAULEY: Was the extent of the
8 myomectomy procedure similar in your control versus
9 your treatment group?

10 DR. diZEREKA: By "extent of the
11 myomectomy," you're referring to?

12 DR. McCAULEY: The incisions, the number
13 of incisions made in the uterus.

14 DR. diZEREKA: The length of the incision
15 was not a piece of data that was collected. The
16 difficulty with that relates to different techniques
17 of performing myomectomies. Let me give you just a
18 couple of quick examples.

19 If a myomectomy is performed with a
20 subserous myoma that protrudes off the surface of the
21 uterus and/or is pedunculated, there is very little
22 deep dissection into the myometrium.

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1 Conversely, if it goes deep into the
2 myometrium and has very little subserous involvement,
3 there's a lot of intrauterine dissection and a lot of
4 trauma.

5 So as a consequence, we thought that the
6 absolute measurement of the incision length would
7 probably not be a useful indicator of the extent of
8 injury that the uterus underwent during the myomectomy
9 procedure.

10 DR. McCAULEY: But the location would make
11 a difference?

12 DR. diZEREGA: Absolutely, and --

13 DR. McCAULEY: And was that looked at
14 specifically?

15 DR. diZEREGA: Yes. We collected data for
16 the anterior surface and for the posterior surface of
17 the uterus, and as is contained in the PMA, the
18 results are very consistent both of the anterior
19 surface, the posterior surface, and the uterus
20 together.

21 DR. McCAULEY: My third question relates
22 to is there any data to suggest that what your product

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1 is actually doing is delaying the formation of
2 adhesions and not really preventing the development of
3 adhesions?

4 If you look at the time span, six to 12
5 weeks, you're right at a period where you may just be
6 shifting the collagen metabolism a little to the left
7 and actually delaying the formation of adhesions as
8 opposed to actually preventing adhesions. Is there
9 any data to suggest that down the line that these
10 patients, either patients or animal models that you've
11 studied, show reformation of these adhesions in say
12 six months, a year later?

13 DR. diZEREGA: A couple of points.

14 And I think that the issue of the healing
15 of the peritoneal cavity is obviously very germane to
16 all that we're talking about here this morning.

17 Over a number of years, and beginning with
18 Herold Ellis and Andrew Raftery that Dr. Talamini was
19 referring to in terms of the healing process, it
20 became known that re-epithelialization of the
21 peritoneum following surgical injury in general is
22 complete at about five to seven days after surgery.

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1 And interestingly, it didn't make a great
2 deal of difference how extensive that surgery was
3 because the re-epithelialization of the peritoneum
4 occurred by island formation on the surface of the
5 peritoneum. So there's a fair amount of homogeneity
6 in re-epithelialization of the surface.

7 You're absolutely right. Remodeling of
8 collagen and other changes in connective tissue
9 proteins goes on for months, but that is beneath the
10 surface, mesothelial layer of these organs, and so the
11 issue of adhesion formation where fibrin is deposited
12 as a result of the surgical procedure and then either
13 undergoes fibrinolysis and is removed or persists and
14 allows for bridges to form when damages to surfaces
15 come in contact, much like two pieces of chewing gum
16 would stick my hands together. That seemed to be the
17 critical point as to whether or not a patient
18 developed a post surgical adhesion.

19 If re-epithelialization of the peritoneum
20 was allowed to progress and if tissue surfaces could
21 be kept apart for five to seven days, adhesion
22 reduction would occur. This has been evaluated in a

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1 number of animal models, different species, different
2 types of surgery, and the results are very much the
3 same. Things that we have done now in the late 1990s
4 really confirm the earlier observations of general
5 surgeons in this area back in the 1970s and early
6 1980s.

7 So it does very much appear to be a
8 barrier effect, just simply keeping the tissues apart
9 long enough, disallowing fiber bridge formation and
10 re-epithelialization to occur, and then have removal
11 of that material secondarily.

12 DR. McCAULEY: But that's only theoretic.

13 DR. diZEREGA: Yes.

14 DR. McCAULEY: It's not practical.

15 DR. diZEREGA: The information that has
16 been determined in animal models has shown with
17 earlier looks versus later looks -- I'm talking about
18 days now -- there are fibrin bands; there are fibrin
19 bridges early on that either go on to form adhesions
20 or are absorbed later on. Hence the five to seven day
21 information has been pretty well confirmed in a
22 variety of animal models and is the subject of a

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1 couple of chapters in my latest textbook.

2 Now, in the clinical arena this has been
3 shown a number of times as well. There have been
4 other devices that have undergone second look
5 evaluation, and this timing event has been a
6 repetitive and recurrent theme.

7 Specific to INTERGEL, and I think one of
8 the most interesting bits of data which is not in our
9 PMA. It's not part of our study. It's actually from
10 a study ongoing in Germany by myomectomy patients, and
11 they're doing those second look laparoscopies much
12 later in time, I think around six months, and their
13 observations of no adhesions. In fact, it's much more
14 impressive than even the results from the sponsor's
15 study, suggesting that as you go forward in time some
16 of these little, filmy bands which may or may not be
17 clinically significant are, in fact, absorbed, and as
18 a consequence the early time points that we've all
19 chosen for our clinical trials are appropriate.

20 CHAIRMAN WHALEN: Dr. Levy.

21 DR. LEVY: I have several questions.
22 Number one: was there any leakage of colored solution

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1 from the incision in these patients?

2 DR. diZEREKA: I believe, Dr. Levy, there
3 was one patient that had an incisional wound healing
4 problem, and I believe that was Thornton's patient.

5 Dr. Thornton was a clinical investigator
6 in this trial, and what I'd like to do is call on Dr.
7 Thornton to describe that incisional problem to you
8 and how it was managed.

9 DR. LEVY: I'm not concerned about the
10 incisional problem. I'm concerned about whether the
11 blinding could have been compromised by leakage of
12 colored solution on gauze dressings or other things.

13 DR. diZEREKA: Oh, I'm sorry. You mean in
14 the acute interval.

15 DR. LEVY: Yes.

16 DR. diZEREKA: No. The answer to that,
17 with exceptions like Dr. Thornton's patient, is no.
18 The peritoneum was closed. The application device is
19 left into the peritoneal cavity. As the abdomen is
20 closed, the peritoneum is closed over the application
21 device and removed, and so the peritoneum is closed
22 entirely. The fascia is closed in the usual way with

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1 a faninsteil incision. The skin is closed. The
2 fluid does not leak out through those barriers.

3 DR. LEVY: Okay. Because lytated
4 (phonetic) Ringer's does whether you close the
5 peritoneum or not, and that may have compromised your
6 blinding.

7 DR. diZEREKA: Yes, and it's interesting
8 you ask about that. In the European area right now,
9 people are using INTERGEL on a regular basis even
10 laparoscopically, and the same types of trochars that
11 might actually allow for some leakage, as you say, of
12 lactated Ringer's postoperatively when the patient is
13 extubated, they're not having that problem with
14 INTERGEL.

15 DR. LEVY: Could you comment on the
16 possibility that your blinding could be compromised
17 because you have leakage in one set of patients and
18 not in another? And obviously the primary surgeon is
19 the person following these patients postoperatively.

20 DR. diZEREKA: I don't know, Barbara. It
21 would be very hard for me to comment on something
22 that's theoretical and didn't happen. I just don't

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1 know what to say about that.

2 DR. LEVY: Well, I'm not saying that your
3 INTERGEL solution leaked, but the lactated Ringer's
4 certainly did.

5 DR. diZEREKA: I don't have any
6 information that it did.

7 DR. LEVY: Okay.

8 DR. diZEREKA: Is there any -- let me just
9 ask our two clinical investigators, Dr. Thornton and
10 Dr. Johns.

11 DR. THORNTON: I'm Melvin Thornton. I'm
12 a principal investigator, and my expenses are
13 reimbursed for this trip.

14 And to answer your question, we did not
15 see any leakage of either the lactated Ringer's or the
16 INTERGEL postoperatively in following the patients.

17 DR. LEVY: And were both the INTERGEL and
18 the lactated Ringer's patients peritoneum was closed
19 in both cases?

20 DR. THORNTON: The way the study was
21 blinded was that for myself at the time that the
22 procedure was done, I exit the room --

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1 DR. LEVY: Right.

2 DR. THORNTON: -- and the surgical
3 assistant, which usually was a resident physician,
4 finished the procedure so that I remained blinded at
5 the whole time.

6 DR. LEVY: Was it part of the protocol
7 that that assistant surgeon would close the peritoneum
8 identically whether there was lactated Ringer's or
9 INTERGEL placed?

10 DR. THORNTON: That's correct.

11 DR. LEVY: Okay. Next question: because
12 70 percent, at least in the United States, of these
13 patients were patients with myomectomies, is there a
14 control for preoperative treatment with Lupron?

15 I know that you're concurrent medications
16 were the same, but what about pre-treatment?

17 DR. diZEREKA: The use of Lupron
18 preoperatively was not part of the information base in
19 these patients. Dr. Diamond has shown I think in a
20 very, very elegant way that GNRH treatment does not
21 make a difference in myomectomy patients undergoing
22 myomectomies with a second look observation in terms

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1 of assessing adhesions.

2 And so as a consequence, we really saw no
3 reason to collect that data.

4 DR. LEVY: My last question for you was as
5 part of your exclusion criteria, you excluded patients
6 that had adhesions to more than 11 sites and you
7 excluded patients where the adhesions had been
8 excised, and I just wondered why. What was the
9 rationale for that when these are the patients who are
10 most likely to benefit from an agent like this?

11 DR. diZEREKA: Two questions. In terms of
12 anatomical site excision, if a patient had an adnexum
13 removed, we found that from a statistical point of
14 view it would confound the data to the point of more
15 difficulty than we thought we'd want to deal with, and
16 so as a consequence, as part of the protocol, if an
17 anatomical site that was part of the study site
18 database was removed, that patient then was excluded
19 from the study.

20 There's just no way to balance for that or
21 to control for that other than just to exclude those
22 patients. It's so infrequent, as you know, in

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1 conservative pelvic surgery. We just thought as an
2 interoperative exclusion it made sense.

3 Now, the other question I think is a very
4 interesting one and one that I've wrestled with a
5 great deal, and that is what patients are appropriate
6 for these types of studies.

7 You raised the question of which patients
8 will benefit from these types of adjuvant therapies.
9 Our view is it's consistent. The types of patients
10 who have massive adhesive disease, the frozen pelvis,
11 those kinds of patients we currently do not recommend
12 conservative surgery for fertility enhancement. Those
13 patients, given the success of in vitro fertilization
14 in all of our centers we think are better served by in
15 vitro fertilization rather than conservative pelvic
16 surgery.

17 Patients who have massive adhesions and
18 pelvic pain, those types of patients, as we all know,
19 the chances of them benefitting in terms of reduction
20 of pelvic pain from that surgical procedure really is
21 small because the adhesions are so extensive in
22 distribution and size.

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1 We thought then that from the types of
2 patients that would actually be receiving this therapy
3 are actually not those patients with severe disease,
4 but rather those patients with either no adhesive
5 disease or mild adhesive disease who are in general
6 having conservative procedures.

7 The idea then is to prevent those very bad
8 outcomes that you see shown by the scoring systems
9 using this type of adjuvant. These are the patients
10 I think this technology is ideally suited for. So in
11 constructing the protocol we tried to find a
12 mathematical or numerical way, much like Dr. DeMets
13 was asking about, to identify patients who would be
14 appropriate in the sense of they will benefit if this
15 product becomes available because they have minimum or
16 no disease.

17 The idea then is to prevent this from
18 happening. As a consequence then we deleted those
19 patients who had more than half of their anatomical
20 sites containing adhesions at the time of the
21 laparotomy.

22 DR. LEVY: Just a comment. That's the

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1 ideal world. In practicality we all know that those
2 are probably exactly the patients that this kind of
3 device would be used for.

4 CHAIRMAN WHALEN: Dr. DeMets for the last
5 question.

6 DR. DeMETS: Actually I think I have three
7 short ones, if that counts.

8 CHAIRMAN WHALEN: Okay.

9 DR. DeMETS: One was was the randomization
10 done within center or stratified by center?

11 DR. diZEREKA: Dr. Hoeler?

12 DR. HOELER: Yes, it was.

13 DR. diZEREKA: Dr. Hoeler's answer is in
14 the affirmative.

15 DR. DeMETS: Okay. Good.

16 There was two ways that the treatment
17 could be applied, either by a third party or a blinded
18 party, or as an alternative that the surgeon doing the
19 first procedure could do the treatment and then not do
20 the second procedure.

21 Could you tell me what the split of that
22 was?

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1 DR. diZEREGA: Dr. Johns.

2 DR. JOHNS: It's not a fact I keep on the
3 top of my head, but I know I have a slide for it. Let
4 me find it.

5 PARTICIPANT: I thought you had all of
6 these facts on top of your head. Found one that you
7 didn't.

8 DR. DeMETS: I have another question which
9 someone can be thinking about. That is there is nine
10 versus 13 patients that were randomized, but not
11 treated. How were those distributed across centers?
12 Was it clustered in any center?

13 DR. JOHNS: I don't recall a clustering.
14 We could look that up for you if you'd like.

15 CHAIRMAN WHALEN: While that's being
16 looked up, is that all of your questions, Dr. DeMets?

17 Dr. Davis had a question.

18 DR. JOHNS: Here's the answer to the
19 blinding question. You can see that the blind
20 investigator was used more often than the blind
21 evaluator approach, but both were used. The blind
22 investigator refers to the use of the surgical

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1 assistant to apply the --

2 DR. DeMETS: Yeah, I understand.

3 DR. JOHNS: Okay.

4 DR. DeMETS: Thank you.

5 CHAIRMAN WHALEN: Dr. Davis.

6 DR. DAVIS: In the safety assessment, the
7 incidence of commonly more than five percent reported
8 adverse events by body system in preferred term, the
9 allergic reaction was ten in the controls and three in
10 the INTERGEL, and I was wondering if -- and that is
11 statistically significant according to your analysis,
12 and could you comment on that? Is this
13 immunosuppressive?

14 DR. diZEREGA: This is one of our favorite
15 observations, and as Dr. Hoeler has taught me, if you
16 do enough analyses, you'll find something's
17 statistically significant.

18 We went back and looked. Of course, this
19 surprised us all. We didn't think it was appropriate
20 for Baxter to put labeling on their lactated Ringer's
21 that it caused an allergic reaction. So we went back
22 and looked at, well, who were these patients and why

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1 was it coded.

2 And it turns out virtually all of the
3 patients were coded for having allergic reactions if
4 they had seasonal allergies, which of course occurred
5 well before the clinical trial.

6 There was another patient that had an
7 allergic reaction to some unrelated medication that
8 she took well after the surgical procedure, and my
9 favorite was a patient who came home a few weeks after
10 her operation and came in contact with a cat that
11 caused an allergic reaction, and as a consequence it
12 was coded as an allergic reaction.

13 So none of the allergic reactions occurred
14 during the surgical procedure, following the surgical
15 procedure in an immediate postoperative interval.
16 Either they were preexisting and occurred, once again,
17 later on as seasonal allergies or were these things
18 that I referred to anecdotally.

19 CHAIRMAN WHALEN: Dr. Roy.

20 DR. ROY: Clinical relevance has been
21 alluded to by referencing studies by others for pain
22 and for fertility. Is there any data that you've been

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